REMARKS

THE LEGAL FRAMEWORK FOR OBVIOUSNESS

The *prima facie* case is a procedural tool which, as used in patent examination, means not only that the evidence of the prior art would reasonably allow the conclusion the Examiner seeks, but also that the prior art compels such a conclusion if the applicant produces no evidence or argument to rebut it. *In re Spada,* 911 F.2d 705 (Fed. Cir. 1990). If examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more, the applicant is entitled to a grant of the patent. *In re Oetiker,* 977 F.2d 1443 (Fed. Cir. 1992).

The following discussion outlines each of the Examiner's rejections and provides evidence and arguments in rebuttal thereof.

THE CLAIM AMENDMENTS

Claim 1 has been amended to more clearly define the invention. Support for the new language to claim 1 is found in the specification at page 24, line 10 to page 26, line 9. This section of the specification explains the use of the two probes to determine the position of interest of a target sequence segment of a target nucleic acid analyte. The identical nature of the probes and the variable position is demonstrated with particularity in the sequences set forth at page 25, line 28 to page 26, line 9.

Claims 1, 7, 10, 16-18, 20, 27-30, 33, 38, 39, and 116-118 have all been amended to correct obvious errors in antecedent basis or merely to rephrase the claims so that the language is more clearly defined. Support for the language of claim 16 is found in the specification at, *inter alia*, page 41. line 12-14; page 44, lines 23-27, and page 45, lines 17-19.

Claim 32 has been canceled without prejudice to pursue the canceled subject matter in a later-filed application.

Claim 115 has been canceled and its subject matter has been incorporated into claim 1.

With the cancellation of claim 115, claim 116 has been amended to depend from claim 1 and the terms "dPTP" and "8-oxo-dGTP" have been changed to "dP" and "8-oxo-dG," which is a more accurate representation of the degenerately pairing nucleotide analogs under the invention. Support for the changes to claims 116-118 is found in the specification at, *inter alia*, page 21, line 23-31 (for dP); page 22, line 27 to page 23, line 3 (for 8-oxo-dG); page 24, line 10 to page 25, line 6; and page 25, line 25 to page 26, line 9.

CLAIM OBJECTION

Claims 20 and 39 were objected because of informalities identified by the Examiner in the claim language. The claims have been amended to correct the identified informalities; accordingly, applicants respectfully request reconsideration and withdrawal of the objections to claims 20 and 39.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 6-15, 18-24, 27-31, 36-39, and 115-118 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The claim rejections have been fully addressed as indicated below.

Claim 1 has been amended to remove the rejected language and has been rewritten to more fully describe the invention.

Claims 10 and 30 have been amended to clarify that the oligonucleotide probe recited therein is the array of oligonucleotide probes from claim 7.

Claim 18, 32, 33, and 38 have been amended so that there is sufficient antecedent basis for all claim terms.

With the amendments to all of the identified claims, the Examiner's indefiniteness rejections have been fully addressed and overcome; accordingly, applicants respectfully request reconsideration and withdrawal of the rejection of the claims as indefinite.

CLAIM REJECTION UNDER 35 U.S.C. § 102(e) - SENAPATHY

Claims 1, 6, 18, 19, 23, 24, 115, 117, and 118 (the Examiner does not identify claims 115, 117, and 118, in the first sentence of the rejection, but discusses these claims in the text of the rejection) stand rejected under 35 U.S.C. § 102(e) as anticipated by Senapathy (U.S. Patent No. 6,521,428). This rejection is respectfully traversed.

As a preliminary matter, applicants note that claim 115 has been canceled and its subject matter has been incorporated into claim 1.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992).

As recited in claim 1, the present invention relates to a method of employing oligonucleotide probes to obtain information on a position of interest on a target sequence segment of a target nucleic acid analyte, the method comprising contacting the target nucleic acid analyte, under hybridizing conditions, with at least two oligonucleotide probes that are identical to each other except for a variable position, wherein on at least one of the at least two oligonucleotide probes, the variable position is occupied by a

degenerately base pairing nucleotide analog and on at least one other of the at least two oligonucleotide probes, the variable position is occupied by a non-degenerately base pairing nucleotide; wherein hybridization of one or all of the at least two oligonucleotide probes to the target sequence segment occurs only if the degenerately base pairing nucleotide analog or the non-degenerately base pairing nucleotide base at the variable position pairs with a complementary nucleotide at the position of interest; and further wherein none of the at least two oligonucleotide probes hybridizes to the target nucleic acid analyte if there is a mismatch between the degenerately base pairing nucleotide analog or the non-degenerately base pairing nucleotide at the variable position and a nucleotide at the position of interest on the target sequence segment.

In a preferred embodiment of the invention, the degenerately base pairing nucleotide is one of dP or 8-oxo-dG (claim 116) and the non-degenerately base pairing nucleotides are A, T, C, and G when the target nucleic acid analyte is DNA (claim 117) and A, U, C, and G when the target nucleic acid analyte is RNA (claim 118). The invention as claimed may be used for various genetic procedures including sequencing the target nucleic acid sequence (claim 6), genetic analysis (claim 21), and allelic analysis (claim 22).

Senapathy teaches a method for sequencing and amplifying nucleic acid templates using a full-length primer with a fixed sequence and a random sequence (col. 3, ll. 7-13). The fixed sequence anchors the primer on the template DNA at its complementary sequence (col. 6, ll. 45-47) and the random sequence provides one full-length primer and many near full-length primer species that bind to complementary flanking sequences (col. 6, ll. 47-50). Because the fixed sequence anchors the primer, primers with mismatches will still bind to the nucleic acid template (col. 6, ll. 39-41). To extend the length of the primers, Senapathy contemplates adding universal bases, such as 5-nitroindole and inosine, which can bind to all four bases (both purines and pyrimidines as noted by the Examiner) as a handle to the 5′ end of the primers (col. 16, ll. 60-61). Senapathy also discloses that the universal bases may be added to the 5′ or 3′ end of the primers, or within the interior sequence of the primers, to expand their binding affinity since the universal bases can bind to any of the four bases at a given nucleotide location (col. 16, ll. 63-66).

Specifically, the method of Senapathy provides the following:

(a) plurality of first primers, each first primer comprising:

(i) a region of fixed nucleotide sequence, and

(ii) a region of randomized nucleotide sequence located 5' to, 3' to, flanking, or interspersed within the region of fixed nucleotide sequence;

(b) annealing the first plurality of primers to a nucleic template, wherein at least one primer anneals to the template; and

(c) extending the first primer with a mixture of dNTPs and ddNTPs to generate a series of nucleic acid fragments;

(d) determining the nucleotide sequence of a first region of the template from the series of nucleic acid fragments.

A second primer can be used to determine a second region of the template.

At claim 1 of Senapathy, it is claimed that the region of different fixed nucleotide sequence has a defined length from about 5 to 15 bases long and a region of randomized nucleotide sequence having a defined length from about 2 to 11 bases long.

It is the Examiner's position that Senapathy anticipates the claimed invention because the two primers of Senapathy can anneal to different locations on a nucleic acid template and the any nucleotide in each first primer that is complementary to the nucleic acid template is a variable nucleotide.

Contrary to the Examiner's assertion, Senapathy does not anticipate the claimed invention for the reasons that follow.

First, while Senapathy discloses a random sequence of 2-11 bases long in the primers disclosed therein, the claimed invention discloses ***a single variable position*** in the claimed oligonucleotide probes.

Second, unlike Senapathy, where the universal bases are located at the handle, in the claimed invention, the degenerately pairing nucleotide analogs are located at the single variable position of the claimed oligonucleotide probe. Thus, unlike Senapathy, where the universal bases in the handle are used to extend the length of the primers disclosed therein and not *to identify a nucleotide at a position of interest*, in the present invention, the degenerately pairing nucleotide analogs are used to determine the nucleotide at a position of interest.

Third, unlike Senapathy where the plurality of primers are annealed to different locations on the nucleic acid template, in the present invention, *the claimed oligonucleotide probes are designed to hybridize to the same target sequence segment.*

Fourth, unlike the claimed invention, where a mismatch at the variable position and the position of interest will not drive hybridization, in Senapathy, hybridization continues even with more than one mismatch between the primers and the complementary sequence of the nucleic acid template (col. 15, ll. 49-54).

Because Senapathy omits numerous elements of independent claim 1, Senapathy does not anticipate this claim. *See, Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, supra.* Because Senapathy does not anticipate independent claim 1, it follows that all claims depending from

claim 1, including claim 6, 18, 19, 23, 24, 117, 118, and the subject matte of canceled claim 115, are also not anticipated by Senapathy. In light of the differences between Senapathy and the claimed invention, applicants respectfully request reconsideration and withdrawal of this rejection.

CLAIM REJECTION UNDER 35 U.S.C. § 102(e) – DRMANAC ET AL.

Claims 1, 6, 7, 9-15, 17, 21-24, 27, 29-31, 33-35, 38, 115, 117, and 118 stand rejected under 35 U.S.C. § 102(e) as anticipated by Drmanac et al. (U.S. Patent No. 6,297,006). This rejection is respectfully traversed.

As a preliminary matter, applicants remind the Examiner that the subject matter of canceled claim 115 has been incorporated into claim 1.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992).

The claimed invention is described in the discussion of the anticipation rejection over Senapathy.

Drmanac et al. teaches a method for detecting a target nucleic acid species wherein the target nucleic acid is applied to an array of probes under conditions such that the probe sequences hybridize to complementary sequences on the target nucleic acid and hybridization is detected by way of the labeled probes.

Specifically, the method of Drmanac et al. includes the steps of:

(a) using an array of probes affixed to a substrate, wherein the array of probes may be a universal sequence; and

(b) a plurality of labeled probes, wherein each labeled probe is selected to have a first nucleic acid sequence complementary to a first portion of a target nucleic acid, and wherein the nucleic acid sequence of at least one probe affixed to the substrate is complementary to a second portion of the nucleic acid sequence of the target, the second portion being adjacent to the first portion;

(c) applying a target nucleic acid to the array under suitable conditions for hybridization of the probe sequences to complementary sequences;

(d) introducing a labeled probe to the array;

(e) hybridizing a probe affixed to the substrate to the target nucleic acid;

(f) affixing the labeled probe to an adjacently hybridized probe in the array; and

(g) detecting the labeled probe affixed to the probe in the array.

Drmanac et al. also discloses that in a preferred aspect, the array of probes affixed to the substrate is a universal set of probes (col. 2, ll. 32-34). At col. 4, ll. 56-64, Drmanac et al. explains that this

universal set is a method by which a more desirable set of probes may be scored. In another preferred aspect, Drmanac et al. discloses that at least two of the probes affixed to the substrate and/or at least two of the labeled probes define overlapping sequences of the target nucleic acid sequences (col. 2, ll. 35-39).

The Examiner takes the position that Drmanac et al. anticipates the claimed invention because any of the nucleotides in the probes of Drmanac et al. are variable nucleotides since they can affix to any complementary base in the target nucleic acid and because Drmanac et al. discloses that the probes affixed to the substrate and the labeled probes have overlapping sequences.

The new language of claim 1 should clarify the Examiner's confusion on the scope of the claims. As noted above in the discussion of Senapathy, the claimed invention relates to the use of at least two oligonucleotides to obtain the identity of an unknown nucleotide at a position on interest of a target sequence segment of a target nucleic acid analyte. The at least two oligonucleotide probes are identical except for a variable position and bind to the same position on the target sequence segment. The presence of a degenerately pairing nucleotide analog in at least one of the probes and a non-degenerately pairing nucleotide on at least one other of the probes determines the identity of the nucleotide. Hybridization of the probes to the analyte only occurs where there is hybridization at the variable position.

Drmanac et al. differs significantly from claimed invention for at least the following reasons.

First, in Drmanac et al. multiple probes are used to attach to different sections of a target nucleic acid and as noted by the Examiner, preferably, the probes have overlapping sequences. By contrast, in the claimed invention, the at least two oligonucleotide probes of the claimed invention are designed to hybridize to the same target sequence segment. Thus, unlike Drmanac et al. where the probes are not similar aside from some overlapping sequences at the 5′ or 3′ ends of the probes, the at least two oligonucleotide probes of the claimed invention are identical save a variable position which is occupied by a degenerately pairing nucleotide analog on at least one probe and a non-degenerately pairing nucleotide on another probe.

Second, while the Examiner asserts that the nucleotides of the Drmanac et al. primers are variable nucleotides because they can bind to any nucleotide in an array of probes (Office Action, page 10, top of the page), the new claim language should now make it clear that the variable position of the claimed oligonucleotide probes is not occupied by just any nucleotide in the at least two oligonucleotide probes; rather, the variable position is occupied a degenerately base pairing nucleotide analog in at least one of the at least two oligonucleotide probes and a non-degenerately pairing nucleotide in at least one other of the at least two oligonucleotide probes. The identity of the position of interest on the target sequence segment is thus determined by comparing the identity of the degenerately pairing nucleotide analog and the non-degenerately pairing nucleotides on the oligonucleotide probes that either do or do not hybridize

to the target sequence segment. Drmanac et al. certainly does not teach, suggest, or contemplate such a variable position in the probes disclosed therein.

Because Drmanac et al. omits numerous elements of independent claim 1, Drmanac et al. does not anticipate this claim. *See, Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, supra.* Because Senapathy does not anticipate independent claim 1, it follows that all claims depending from claim 1, including claim 6, 7, 9-15, 17, 21-24, 27, 29-31, 33-35, 38, 117, 118, and the subject matter of canceled claim 115, are also not anticipated by Drmanac et al. In light of the differences between Drmanac et al. and the claimed invention, applicants respectfully request reconsideration and withdrawal of this rejection.

CLAIM REJECTION UNDER 35 U.S.C. § 103 – SENAPATHY IN VIEW OF SANTAMARIA ET AL.

Claims 21 and 22 stand rejected under 35 U.S.C. § 103(a) as obvious over Senapathy as applied to claims 1, 6, 18, 19, 23, 24, 115, 117, and 118 above, and further in view of Santamaria et al. This rejection is respectfully traversed.

Claims 21 and 22 ultimately depend from claim 1.

To establish a *prima facie* case of obviousness, three criteria must be met: first, the prior art reference must teach or suggest the claimed combination; second, the Office must show that the ordinary artisan would be motivated to modify the reference or to combine the reference teachings; and third, there must be a showing that the ordinary artisan would have a reasonable expectation of success at arriving at the claimed combination based *solely* on the teachings of the cited prior art reference. *In re Rouffet,* 149 F.3d 1350, 1357 (Fed. Cir. 1998); *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991).

The discussion in traverse of the Senapathy anticipation rejection explains why Senapathy does not teach the claimed invention. Senapathy also does not render the claimed invention obvious because there is no suggestion in Senapathy that would motivate the ordinary artisan to modify the primers of Senapathy to be like the oligonucleotide primers of the claimed invention.

As noted above, the individual primers of Senapathy are intended to attach to different parts of the nucleic acid template. The fixed sequence in the primers is used to ensure that the primers attach to one location on the nucleic acid template (col. 7, ll. 31-34), the random sequence used to determine the sequence adjacent to the fixed sequence (col. 5. ll. 40-44), and the 5-nitroindole and iosine universal bases, which bind to all four nucleotides, are used in the handle solely for the purpose of extending the primers for PCR or 5′, 3′, or within the primers to enhance the binding affinity of the primers (col. 16, ll. 58-66).

At col. 7, ll. 31-34, Senapathy states that the purpose of the invention is to provide a full length primer with a capability to bind with specific complementarity to one location on a template DNA whose sequence is unknown.

There is no suggestion in Senapathy that the primers disclosed therein may be used to attach to one single target sequence segment and that the random sequence may be used to identify a position of interest on a target sequence segment. As stated in Senapathy, the primers disclosed therein are designed to attach to the nucleic acid template with the fixed region used to identify the location of the primer on the nucleic acid template and the random region used to provide a full length primer (col. 7, l.66 to col. 8, l. 10).

Furthermore, even if the ordinary artisan were to modify the primers of Senapathy with the degenerately pairing nucleotide analogs dP or 8-oxo-dG, all the ordinary artisan would expect would be enhanced binding affinity of the primers as a result of the dP being capable of binding to both A and G and 8-oxo-dG being capable of binding to both T and G. Thus, even with this change, the ordinary artisan would not have a reasonable expectation of successfully arriving at the claimed invention.

The foregoing analysis demonstrates that Senapathy alone ***does*** not render the invention of claim 1 obvious.

Notwithstanding the foregoing, with respect to the subject matter of claim 22, the Examiner acknowledges that Senapathy does not teach or suggest that the method disclosed therein may be used for genetic analysis such as allelic analysis. The Examiner thus cites Santamaria et al. for the teaching that the primers of Senapathy may be used for genetic analysis and allelic analysis.

Santamaria et al. teaches a method for genotyping polymorphic systems by PCR of cDNA or genomic DNA. The method of Santamaria et al. involves amplifying the alleles carried by any given individual at a gene locus or loci of interest by PCR with conserved and non-conserved oligonucleotide primers. The PCR products are sequenced followed by evaluation of the resulting nucleic acid ladders to determine the genotype of sample nucleic acid.

The teachings of Santamaria et al. do not correct the deficiencies of Senapathy. Because Senapathy fails to teach or suggest the invention as recited in claim 1, the additional teachings of Santamaria et al. will not serve to render claims 21 and 22 obvious.

Because Senapathy in view of Santamaria et al. do not render claims 21 and 22 obvious, applicants respectfully request reconsideration and withdrawal of this rejection.

CLAIM REJECTION UNDER 35 U.S.C. § 103(a) – DRMANAC ET AL. IN VIEW OF VESNAVER ET AL.

Claim 16 stands rejected under 35 U.S.C. § 103(a) as obvious over Drmanac et al. as applied to claims 1, 6, 7, 9-15, 17, 21, 24, 27, 29-31, 33-35, 38, 115, 117, and 118 and further in view of Vesnaver et al. This rejection is respectfully traversed.

Claim 16 ultimately depends from claim 1.

To establish a *prima facie* case of obviousness, three criteria must be met: first, the prior art reference must teach or suggest the claimed combination; second, the Office must show that the ordinary artisan would be motivated to modify the reference or to combine the reference teachings; and third, there must be a showing that the ordinary artisan would have a reasonable expectation of success at arriving at the claimed combination based *solely* on the teachings of the cited prior art reference. *In re Rouffet,* 149 F.3d 1350, 1357 (Fed. Cir. 1998); *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991).

The discussion in traverse of the Drmanac et al. anticipation rejection explains why Drmanac et al. does not teach the claimed invention. Drmanac et al. also does not render the claimed invention obvious because there is no suggestion in Drmanac et al. that would motivate the ordinary artisan to modify the primers of Drmanac et al. to be like the oligonucleotide primers of the claimed invention.

As noted above, the individual arrayed primers of Drmanac et al. are intended to attach to different parts of the nucleic acid template and in a preferred embodiment, each of the adjacent primers overlap at the 5′ or 3′ ends of the primer.

There is no suggestion in Drmanac et al. that would motivate the ordinary artisan to apply the primers of Drmanac such that each of the individual primers is identical to the next, save a single variable position that is occupied by a degenerately pairing nucleotide analog on at least one primer, and as such is intended to hybridize to the same target sequence for the purpose of obtaining information on a position of interest of the target sequence segment, which is a position complementary to the variable position on the individual primers.

Furthermore, even were the ordinary artisan to modify the primers of Drmanac et al. such that they included the degenerately pairing nucleotides dP and 8-oxo-dG of the claimed invention, the ordinary artisan would only expect enhanced binding affinity of the primers as a result of the dP being capable of binding to both A and G and 8-oxo-dG being capable of binding to both T and G. Thus, even with this change, the ordinary artisan would not have a reasonable expectation of successfully arriving at the claimed invention.

The foregoing analysis demonstrates that Drmanac et al. alone ***does*** not render the invention of claim 1 obvious.

Notwithstanding the foregoing, with respect to the subject matter of claim 16, the Examiner acknowledges that Drmanac et al. does not teach or suggest that the hybridized nucleic acid disclosed therein may be detected by measuring the heat of hybridization. The Examiner thus cites Vesnaver et al. for the teaching that DNA duplex formation and disruption may be determined by measuring the thermodynamic profile of a hybridized sequence.

The teachings of Vesnaver et al. do not correct the deficiencies of Drmanac et al. Because Drmanac et al. fails to teach or suggest the invention as recited in claim 1, the additional teachings of Santamaria et al. will not serve to render claim 16 obvious.

Because Drmanac et al. in view of Vesnaver et al. do not render claim 16 obvious, applicants respectfully request reconsideration and withdrawal of this rejection.

CLAIM REJECTION UNDER 35 U.S.C. § 103(a) – DRMANAC ET AL. IN VIEW OF DATTAGUPTA

Claim 20 stands rejected under 35 U.S.C. § 103(a) as obvious over Drmanac et al. as applied to claims 1, 6, 7, 9-15, 17, 21, 24, 27, 29-31, 33-35, 38, 115, 117, and 118 and further in view of Dattagupta. This rejection is respectfully traversed.

Claim 20 ultimately depends from claim 1.

The legal standard for obviousness and arguments supporting the nonobviousness of the invention as recited in claim 1 over Drmanac et al. are set forth in traversal of the rejection of the claimed invention over Drmanac et al. in view of Vesnaver et al. The same arguments set forth in that discussion apply here; those arguments concluding with the assertion that Drmanac et al. alone does ***not*** teach or suggest the claimed invention, and in particular, the invention as recited in independent claim 1.

With respect to the subject matter of claim 20, the Examiner acknowledges that Drmanac et al. does not teach or suggest that the hybridized nucleic acids disclosed therein may be amplified by RNA replicase enzyme. The Examiner thus cites Dattagupta for the teaching that target sequences may be transcripted in the presence of a RNA polymerase, such as for example, RNA replicase enzyme and an appropriate ribonucleoside triphosphate (rNTP).

The teachings of Dattagupta do not correct the deficiencies of Drmanac et al. Because Drmanac et al. fails to teach or suggest the invention as recited in claim 1, the additional teachings of Dattagupta will not serve to render claim 20 obvious.

Because Drmanac et al. in view of Dattagupta do not render claim 20 obvious, applicants respectfully request reconsideration and withdrawal of this rejection.

CLAIM REJECTION UNDER 35 U.S.C. § 103(a) – DRMANAC ET AL. IN VIEW OF WALT ET AL.

Claims 8, 28,36, and 37 stand rejected under 35 U.S.C. § 103(a) as obvious over Drmanac et al. as applied to claims 1, 6, 7, 9-15, 17, 21, 24, 27, 29-31, 33-35, 38, 115, 117, and 118 and further in view of Walt et al. This rejection is respectfully traversed.

Claims 8, 28, 37, and 37 ultimately depend from claim 1.

The legal standard for obviousness and arguments supporting the nonobviousness of the invention as recited in claim 1 over Drmanac et al. are set forth in traversal of the rejection of the claimed invention over Drmanac et al. in view of Vesnaver et al. The same arguments set forth in that discussion apply here; those arguments concluding with the assertion that Drmanac et al. alone does ***not*** teach or suggest the claimed invention, and in particular, the invention as recited in independent claim 1.

With respect to the subject matter of claims 8, 28, 36, and 37, the Examiner appears to assert that the subject matter of these four claims, which relate to the use of beads or particles to which the oligonucleotides may attach when in an array (claims 8 and 28) and to the functionalization of the substrate surface of the array to enhance hybridization, is disclosed in Drmanac et al., nevertheless, the Examiner nonetheless cites Walt et al. for the same teachings. Applicants have reviewed Drmanac et al. and have found a teaching at col. 8, ll. 17-22, that enhanced washing conditions may increase hybridization stringency, but were unable to find any teachings in Drmanac et al. relating to the use of beads or particles or surface modification of the substrate. Applicants acknowledge that Walt et al. discloses an array comprised of beads; however, in Walt et al., the oligonucleotides, rather than a plurality of identical target nucleic acid analyte sequences are attached to the beads (*see, e.g.*, para. 0051). Walt et al. also discloses surface modification of the substrate disclosed therein; however, in Walt et al. the surface modification is to increase the area so that additional microspheres may be inserted in the modified substrate surface to produce extremely high density arrays (*see, e.g.*, paras. 0065-0073).

Regardless of the teachings of Drmanac et al. and Walt et al. with respect to the use of beads and functionalized substrates for hybridization purposes, these teachings will not serve to render claims 8, 28, 36, and 37 obvious because, as explained in the discussion of the Drmanac et al. anticipation rejection and the Drmanac et al. in view of Vesnaver et al. obviousness rejection, Drmanac et al. fails to teach or suggest the invention as recited in claim 1.

Because Drmanac et al. alone or Drmanac et al. in view of Walt et al. do not render claims 8, 28, 36, and 37 obvious, applicants respectfully request reconsideration and withdrawal of this rejection.

CLAIM REJECTION UNDER 35 U.S.C. § 103(a) – DRMANAC ET AL. IN VIEW OF ACKLEY

Claim 39 stands rejected under 35 U.S.C. § 103(a) as obvious over Drmanac et al. as applied to claims 1, 6, 7, 9-15, 17, 21, 24, 27, 29-31, 33-35, 38, 115, 117, and 118 and further in view of Ackley. This rejection is respectfully traversed.

Claim 39 ultimately depends from claim 1.

The legal standard for obviousness and arguments supporting the nonobviousness of the invention as recited in claim 1 over Drmanac et al. are set forth in traversal of the rejection of the claimed invention over Drmanac et al. in view of Vesnaver et al. The same arguments set forth in that discussion apply here; those arguments concluding with the assertion that Drmanac et al. alone does ***not*** teach or suggest the claimed invention, and in particular, the invention as recited in independent claim 1.

With respect to the subject matter of claim 39, the Examiner acknowledges that Drmanac et al. does not teach or suggest that hybridization may be enhanced through the use of an integrated semiconductor chip that controls electric potential at the substrate surface. The Examiner thus cites Ackley for the teaching of enhanced hybridization techniques by using enhanced electric field enhancements (col. 1, ll. 33-35).

The teachings of Ackley do not correct the deficiencies of Drmanac et al. Because Drmanac et al. fails to teach or suggest the invention as recited in claim 1, the additional teachings of Ackley will not serve to render claim 39 obvious.

Because Drmanac et al. in view of Ackley do not render claim 39 obvious, applicants respectfully request reconsideration and withdrawal of this rejection.

CLAIM REJECTION – DRMANAC ET AL. IN VIEW OF HILL ET AL.

Claim 116 stands rejected under 35 U.S.C. § 103(a) as obvious over Drmanac et al. in view of Hill et al. This rejection is respectfully traversed.

Claim 116 ultimately depends from claim 1.

The legal standard for obviousness and arguments supporting the nonobviousness of the invention as recited in claim 1 over Drmanac et al. are set forth in traversal of the rejection of the claimed invention over Drmanac et al. in view of Vesnaver et al. The same arguments set forth in that discussion apply here; those arguments concluding with the assertion that Drmanac et al. alone does ***not*** teach or suggest the claimed invention, and in particular, the invention as recited in independent claim 1.

With respect to the subject matter of claim 116, the Examiner acknowledges that Drmanac et al. does not teach or suggest the degenerately pairing nucleotide analogs dP and 8-oxo-dG. The Examiner

thus cites Hill et al. for the teaching that the synthetic nucleotide analog dP may be used as a degenerate base.

The teachings of Hill et al. do not correct the deficiencies of Drmanac et al. Because Drmanac et al. fails to teach or suggest the invention as recited in claim 1, the additional teachings of Hill et al. will not serve to render claim 116 obvious.

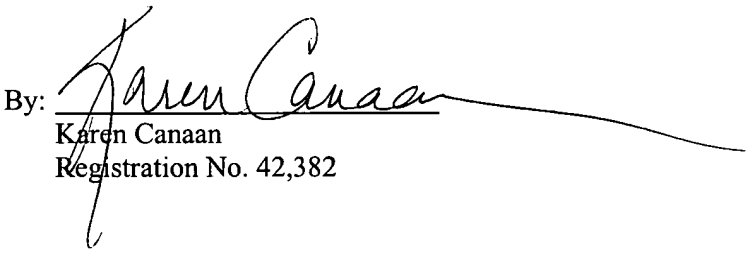
Because Drmanac et al. in view of Hill et al. do not render claim 116 obvious, applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

Because all of the claim objections and claim rejections set forth by the Examiner have been addressed and fully rebutted with the amendments and arguments set forth in this paper, applicants respectfully request withdrawal of all claim objections and rejections and passage of this application to a patent grant. *See, In re Oetiker, supra.*

Should the Examiner have any questions relating to this paper, he is welcome to contact the undersigned attorney at 650-330-4913 or at canaan@reedpatent.com.

Respectfully submitted,

By: 
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